

National Cancer Institute Research on Childhood Cancers

In the United States in 2005, approximately 9,510 children under age 15 will be diagnosed with cancer and about 1,585 children will die from the disease (1). Although this makes cancer the leading cause of death by disease among U.S. children 1 to 14 years of age, cancer is still relatively rare in this age group with, on average, 1 to 2 children developing the disease each year for every 10,000 children in the United States.

Among the 12 major types of childhood cancers, leukemias (blood cell cancers) and brain and other central nervous system tumors account for over one-half of the new cases. About one-third of childhood cancers are leukemias. The most common type of leukemia in children is acute lymphoblastic leukemia. The most common solid tumors are brain tumors (e.g., gliomas and medulloblastomas), with other solid tumors (e.g., neuroblastomas, Wilms' tumors, and sarcomas such as rhabdomyosarcoma) being less common.

Over the past 20 years, there has been some increase in the incidence of children diagnosed with all forms of invasive cancer, from 11.5 cases per 100,000 children in 1975 to 14.6 per 100,000 children in 2002. During this same time, however, death rates declined dramatically and 5-year survival rates increased for most childhood cancers. For example, the 5-year survival rates for all childhood cancers combined increased from 55.9 percent in



1974–1976 to 78.6 percent in 1995–2001 (2). This improvement in survival rates is due to significant advances in treatment, resulting in cure or long-term remission for a substantial proportion of children with cancer.

Long-term trends in incidence for leukemias and brain tumors, the most common childhood cancers, show patterns that are somewhat different from the others. Childhood leukemias appeared to increase in incidence in the early 1980s, with rates in the preceding years at fewer than 4 cases per 100,000. Rates in the succeeding years have shown no consistent upward or downward trend and have ranged from 3.7 to 4.8 cases per 100,000 (2).

For childhood brain tumors, the overall incidence rose from 1975 through 2002 (from 2.3 to 3.5 per 100,000), with the greatest increase occurring from 1983 through 1986. An article in the September 2, 1998, issue of the *Journal of the National Cancer Institute* suggests that the rise in incidence from 1983 through 1986 may not have represented a true increase in the number of cases, but may have reflected new forms of imaging equipment (magnetic resonance imaging or MRI) that enabled visualization of brain tumors that could not be easily visualized with older equipment. Other important developments during the 1983–1986 period included the changing classification of brain tumors, which resulted in tumors previously designated as “benign” being reclassified as “malignant,” and improvements in neurosurgical techniques for biopsying brain tumors.

The causes of childhood cancers are largely unknown. A few conditions, such as Down syndrome, other specific chromosomal and genetic abnormalities, and ionizing radiation exposures, explain a small percentage of cases.

Environmental causes of childhood cancer have long been suspected by many scientists but have been difficult to pin down, partly because cancer in children is rare, and partly because

it is so difficult to identify past exposure levels in children, particularly during potentially important periods such as pregnancy or even prior to conception. In addition, each of the distinctive types of childhood cancers develops differently—with a potentially wide variety of causes and a unique clinical course in terms of age, race, gender, and many other factors.

A monograph based on data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program was published in 1999 on U.S. trends in incidence, mortality, and survival rates of childhood cancers. In the monograph, information about known, suspected, and possible risk factors is summarized in more detail. It is available at <http://seer.cancer.gov/publications/childhood/> on the Internet. More up-to-date incidence, mortality, and survival information for children (<15 and <20 years of age) is available at http://seer.cancer.gov/csr/1975_2002/sections.html on the Internet, in sections 28 and 29.

Results of Recent Studies Supported by the NCI

For several decades, the NCI has supported national and international collaborations devoted to studying causes of cancer in children. Some of the key findings from recent studies include:

- High levels of ionizing radiation from accidents or from radiotherapy have been linked with increased risk of some childhood cancers;
- Children treated with chemotherapy and radiation therapy for certain forms of childhood and adolescent cancers, such as Hodgkin's disease, brain tumors, sarcomas, and others, may develop a second primary malignancy;
- Low levels of radiation exposure from radon were not significantly associated with childhood leukemias;
- Ultrasound use during pregnancy has not been linked with childhood cancer in numerous large studies;
- Residential magnetic field exposure from power lines was not significantly associated with childhood leukemias;
- Certain types of chemotherapy, including alkylating agents or topoisomerase II inhibitors (e.g., epipodophyllotoxins), may cause increased risk of leukemia;

- Pesticides have been suspected to be involved in the development of certain forms of childhood cancer based on interview data. However, interview results have been somewhat inconsistent, and have not yet been validated by physical evidence of pesticides in the child's body or environment;
- No consistent findings have been observed linking specific occupational exposures of parents to the development of childhood cancers;
- Several studies have found no link between maternal cigarette smoking before pregnancy and childhood cancers, but increased risks were related to the father's prenatal smoking habits in studies in the United Kingdom and China;
- Little evidence has been found to link specific viruses or other infectious agents to the development of most types of childhood cancers, though investigators worldwide are exploring the role of exposure of very young children to some common infectious agents that may protect children from, or put them at risk for, developing certain leukemias;
- Recent research has shown that children with AIDS, like adults with AIDS, have an increased risk of developing certain cancers, predominantly non-Hodgkin's lymphoma and Kaposi's sarcoma. These children also have an additional risk of developing leiomyosarcoma (a type of muscle cancer);
- Specific genetic syndromes, such as the Li-Fraumeni syndrome, neurofibromatosis, and several others, have been linked to an increased risk of specific childhood cancers.

NCI's Current Research on Childhood Cancer

NCI is currently funding a large portfolio of studies (<http://researchportfolio.cancer.gov/>) looking at the causes and most effective treatments for childhood cancers at an estimated cost of \$166 million for Fiscal Year 2004. Ongoing investigations include:

- **Studies to identify causes of the cancers that develop in children**
 - The Children's Oncology Group (<http://www.childrensoncologygroup.org>) is evaluating potential risk factors for a variety of childhood cancers. Very large studies of childhood acute lymphoblastic leukemia, acute myeloid leukemia, non-Hodgkin's lymphoma, primitive neuroectodermal tumors of the brain, astrocytoma, and neuroblastoma have recently been completed, while investigations of germ cell tumors are ongoing. These studies have included evaluation of diverse categories of suspected and possible risk factors including exposures linked to infectious agents (e.g., enrollment in daycare, spacing of siblings, and infectious diseases contracted during the first 12 months of life); parental occupational exposures to radiation or chemicals; parental medical conditions during pregnancy or before conception; parental, fetal, or childhood exposures to environmental toxins such as pesticides, solvents, or other household chemicals; maternal

diet during pregnancy; early postnatal feeding patterns and dietary factors; reproductive history and other reproductive factors; and familial and genetic factors.

- The role of maternal exposures to oral contraceptives, fertility drugs, and diethylstilbestrol (DES) is being investigated in several ongoing studies.
 - Researchers are looking at the role of familial and genetic disorders.
 - The cancer risk of HIV-infected children is under investigation.
 - The Childhood Cancer Survivor Study (see below) is evaluating the risks of second cancers related to radiation therapy and chemotherapy received by survivors of childhood cancer as part of treatment for their primary cancer.
- **Monitoring of U.S. and international trends in incidence and mortality rates for childhood cancers**

By identifying places where high or low cancer rates occur, researchers can uncover patterns of cancer that provide important clues for further in-depth studies into the causes and control of cancer.

- **Studies to better understand the biology of childhood cancer, with the hope that this understanding will lead to new treatment approaches that target critical cellular processes required for cancer cell growth and survival**

Researchers are investigating fundamental cellular processes, such as signal transduction, cell cycle control, transcriptional regulation, and tumor suppressor gene inactivation, to develop new prevention and treatment strategies.

- **Projects designed to improve the health status of survivors of childhood cancers**

A major component of NCI's survivorship research efforts is the Childhood Cancer Survivor Study (CCSS), which was created to learn about the long-term effects of cancer and its therapy on childhood cancer survivors (<http://www.cancer.umn.edu/ltfu#CCSS>). This knowledge may be useful in designing future treatment protocols and intervention strategies that increase survival and minimize harmful health effects. In addition, CCSS serves to educate survivors about the potential impacts of cancer diagnosis and treatment on their health. CCSS includes 14,000 childhood cancer survivors diagnosed with cancer before the age of 20 between 1970 and 1986, and approximately 3,500 siblings of survivors who serve as control subjects for the study. The CCSS cohort was assembled through the efforts of 27 participating centers in the United States and Canada and has been coordinated by investigators at the University of Minnesota. Funded by the NCI, the study was initiated in 1993 and completed in 2004.

- **Clinical trials to identify superior treatments for childhood cancers, thereby leading to improved survival rates for children with cancer**

Each year about 4,000 children enter one of approximately 100 ongoing clinical trials sponsored by NCI. The following groups are conducting these trials:

- Children's Oncology Group (COG) (<http://www.childrensoncologygroup.org>). COG is supported by NCI to conduct clinical trials devoted exclusively to children and adolescents with cancer at more than 200 member institutions, including cancer centers of all major universities, teaching hospitals throughout the United States and Canada, and sites in Europe and Australia. COG was formed in 2000 by the merger of four children's cancer cooperative groups in order to accelerate the search for a cure for the cancers of children and to make it possible for children with cancer, regardless of where they live, to have access to state-of-the art therapies and the collective expertise of world-renowned pediatric specialists.
- Pediatric Brain Tumor Consortium (PBTC) (<http://www.pbtc.org>). The primary objective of the PBTC is to rapidly conduct phase I and II clinical evaluations of new therapeutic drugs, intrathecal agents (agents injected into the cerebrospinal fluid), delivery technologies, biological therapies, and radiation treatment strategies in children up to 21 years of age with primary central nervous system (CNS) tumors. The PBTC includes nine leading academic institutions with extensive experience in the design and conduct of clinical trials for children with brain tumors. Another objective of the PBTC is to develop and coordinate innovative neuro-imaging techniques. Results from PBTC studies are made available to large international collaborative groups for confirmatory phase II and multi-agent phase III clinical trials.
- New Approaches to Neuroblastoma Therapy Consortium (NANT) (<http://www.nant.org>). NANT is a consortium of university and children's hospitals funded by the NCI to test promising new therapies for neuroblastoma. NANT members constitute a group of closely collaborating investigators linked with laboratory programs where novel therapies for high-risk neuroblastoma are being developed. The group conducts early trials to test new drugs and new combinations of drugs so promising therapies can be tested nationally.
- **Evaluations of new drugs that may be more effective against childhood cancers and that may have less toxicity for children**

The Children's Oncology Group Phase I/Pilot Consortium is a major component of the NCI's pediatric drug development program (<http://www.childrensoncologygroup.org>). The primary objective of the consortium is to develop and implement pediatric phase I and pilot studies to promote the integration of advances in cancer biology and therapy into the treatment of childhood cancer. The consortium includes approximately 20 institutions that carefully monitor the drugs for toxicity and safety. After their initial evaluation for safety in children by the consortium, the agents and regimens can then be studied within the larger group of COG institutions to determine their role in the treatment of specific childhood cancers.

NCI's Future Investments

NCI is supporting a pilot study by the COG to evaluate the feasibility of establishing a Childhood Cancer Research Network that would create a national registry of children with

cancer, including a tissue bank for tumor and blood specimens, to be used for identifying environmental and other causes of childhood cancer. This initiative seeks to build on the unique national clinical trials system for treating children with cancer.

Selected References

1. American Cancer Society (2005). *Cancer Facts and Figures 2005*. Retrieved March 29, 2005, from:
<http://www.cancer.org/downloads/STT/CAFF2005f4PWSecured.pdf>.
2. Ries LAG, Eisner MP, Kosary CL, et al. (eds). *SEER Cancer Statistics Review, 1975–2002*, National Cancer Institute. Bethesda, MD, 2005
(http://seer.cancer.gov/csr/1975_2002).

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Related Resources

Publications (available at <http://www.cancer.gov/publications>)

- National Cancer Institute Fact Sheet 1.21, *Care for Children and Adolescents with Cancer: Questions and Answers*.
- National Cancer Institute Fact Sheet 2.11, *Clinical Trials: Questions and Answers*

National Cancer Institute (NCI) Resources

Cancer Information Service (toll-free)

Telephone: 1–800–4–CANCER (1–800–422–6237)

TTY: 1–800–332–8615

Online

NCI's Web site: <http://www.cancer.gov>

LiveHelp, NCI's live online assistance:

<https://cissecure.nci.nih.gov/livehelp/welcome.asp>

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